ATTACHMENT 9: MAJOR MILESTONES AND PROPOSAL TOPICS

1. MAJOR MILESTONES

SCHEDULE FOR CHEMICAL AND BIOLOGICAL TECHNOLOGIES DEPARTMENT NEW INITIATIVES FY2014-2017 PROGRAM	
DATE	**EVENT**
7 March 2013	BAA announced in FedBizOpps website
7 March 2013	Begin registration at the DTRA proposal submission website
7 March 2013	DTRA proposal submission website opens for receipt of Quad Chart/White Paper
29 March 2013	Deadline to submit questions
5 April 2013	Questions and Answers posted at FedBizOpps
10 April 2013 No Later than 2:00 p.m. EDT	Phase I proposal receipt deadline (Quad Chart/White Paper)
24 May 2013	Phase II proposals invited; non-selection notifications will follow within 2 weeks.
24 June 2013 No Later than 2:00 p.m. EDT	Phase II proposal receipt deadline
On or About 2 August 2013	Notification of selection or non-sent to Offerors
On or About 21 February 2014	Estimated First Award Date ("on or about" is used since this is an estimate)
Awards expected to begin approx. 150 days following initiation of negotiations [1, 2]	

Notes:

1. Actual award dates will vary based on complexity, statutory requirements, quality of proposal, pricing considerations, DCAA audits of proposed rates, type of instrument, number of awards, receipt of funding, and other considerations. All dates are subject to change.
2. Awards will be made subject to the availability of funds. All Offerors will be invited to begin negotiations upon notification of intent to award, and awards will be made as funds are available.

The topics and timelines published in the initial issuance are as stated above. In the future, as ongoing or new technology requirements may necessitate amendment of the BAA to include new topics. At the time that topics are amended, new proposal submission milestones will be specified. Refer to Section 3.1 of the BAA.

1. PROPOSAL TOPICS

The DOD is interested in soliciting proposals in the following areas of Chemical and Biological Defense. The intent of these topics is to identify technologies that fill identified capability needs in the DOD Chemical and Biological Defense Program. The level of detail provided for each specific technology area and sub-area or order in which they appear is not intended to convey any information regarding relative priority.

Topic: NTABAA1417CBS-01

Enabling Science – Novel Threat Research - Rapidly characterize Chemical threat properties based on a pre-established prioritized list of critical parameters

Objective: Provide necessary data to support development of countermeasures and tactics, techniques and procedures (TTPs) against technological surprise.

Title: Resuspension Factors and Atmospheric Persistence of CB Particulate and Aerosol Threats.

This is a topic to determine the particulate resuspension and half-life in the atmosphere for chemical agents. Persistence is defined as molecular and physical changes that effect survivability, transport and identification in the environment. Such knowledge may then be used to:

- Establish set baselines to assess resuspension risk as a function of specific characteristics of the particulate, the material and the environment
- Predict the transport of chemical agent particulates from contaminated surfaces or sites
- Establish set baselines for half-life and information hazard management protocols
- Inform property characterization and factors required in modeling, simulation and prediction of agent half-life in the environment
- Estimate concentration of agent available for exposure in the atmosphere

Key questions and knowledge sought include but are not limited the following:

(1) Characterization of atmospheric half-life and resuspension rates of chemical threats
   a. Understanding/characterizing the relevant agent properties of the agents that regulate persistence in the atmosphere including both molecular/physical and processing (e.g. diameter, agglomeration charge…)
   b. Characterize atmospheric half-life and resuspension rates of chemical threat agents and predict resuspension rates and atmospheric persistence based on variety of environmental scenarios (e.g. temperature, air quality, humidity, UV)
   c. Identification of key transport particle processes and forces for both mechanical and environmental including but not limited to wind car traffic, human traffic, precipitation and washing
   d. Understanding the role of deposition/ dissemination on resuspension or persistence.

(2) Linking laboratory studies on persistence and resuspension with real world information
   a. Develop data correlation algorithms to link laboratory data with real world scenarios
      i. Leveraging existing data
      ii. Linking chemical agents with environmental samples and real world examples
   b. Validate correlation factors for DoD particulates of interest against actual environmental monitoring samples using relevant laboratory analyses
   c. Validate laboratory studies in real world environments and scenarios
   d. Development of adequate validated simulants for outdoor assessments of persistence and or resuspension

Proposals can be up to 3 years with the aim of characterizing chemical agent resuspension and atmospheric persistence. This information will then be transitioned to other DOD and USG programs responsible for determination of human exposure factors.

Metrics: Proposals will be judged according to scientific significance of the proposal as follows:

(1) The contribution the research makes to the approach, method, and understanding of the risk associated with chemical agent resuspension.
(2) The soundness of the proposed methodology
(3) The adequacy and thoroughness of the theoretical background and best use of existing data/practices to determine resuspension factors
(4) The overall return on investment
(5) The viability of the proposed effort (can the specific steps and milestones be carried out with the indicated resources).

Data generated is required to be independently validated and proposals that to do not include this will be considered noncompliant.

Topic: NTABAA1417CBS-02

Thrust Two – Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health)

To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposed efforts should be designed to have a 1 year base period and up to four option years, for a maximum of 5 years.

Title: Pretreatments for CWA/NTA Exposure

This topic is for novel solutions for the pretreatment of CWA/NTA exposure. Candidate compounds can include one of the following approaches:

1. Biologic candidates. These candidates include antibodies or enzymes that can neutralize CWA/NTA either through covalent sequestration or hydrolysis. Proposed solutions that merely bind in a non-covalent or non-hydrolyzing manner will not be considered responsive to this topic. Additionally, preference will be given to proposals that address in vivo stability, potential immunogenicity, delivery and manufacturing scale/cost of the most promising candidates.

2. Small molecule candidates. Novel small molecules are sought that are capable of either (1) safely and effectively hydrolyzing and/or neutralizing CWAs/NTAs or (2) allosterically modulating target proteins/enzymes to promote protection against CWAs/NTAs. Proposals that address protein/enzyme reactivators or their derivatives will not be considered responsive to this topic.

Development strategies may include, but are not limited to, high-throughput screening methods and rational design through novel computational or structural methods.

Metric: The mechanism of action of the candidate compounds must be established. Solutions must be effective against multiple CWAs/NTAs and/or surrogates. If surrogates are used, the proposal must justify the choice of surrogate. In vitro, candidates must demonstrate fast ($k_{cat}/K_m > 1x10^7\ M^{-1}min^{-1}$) and effective hydrolysis or covalent modification of CWA/NTA or surrogate to justify their continued development. In vivo, they must cause no adverse effects when administered and provide protection against 2-5xLD_{50} CWA/NTA or surrogate exposure for 10 days.

Topic: NTABAA1417CBS-03

Thrust Two – Adaptive Medical Countermeasures and Technologies Biological Pretreatments

Objective: Defeat chemical and biological threats to the warfighter and nation through translational medicine (SHIELD and SUSTAIN mission capability and health).

To reach this goal, proposals that characterize and evaluate novel candidates against specified threat agents and address the topics presented below are desired. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Title: Centrally Active Nerve Agent Treatment Systems (CANATs)

The currently fielded nerve agent treatment regimen has limited efficacy in the brain therefore it is unable to prevent the neuropathology and behavior deficits observed with nerve agent CNS-exposure. This topic seeks to fill this gap with the development of a novel reactivator that is capable of reactivating brain acetylcholinesterase. *Proposals that emphasize delivery of already developed oximes will not be considered. Proposals that focus on the reactivation of butrylcholinesterase will not be considered.*

Metric: Proposals should demonstrate the compound has a high probability of crossing the human blood-brain-barrier by demonstrating adequate membrane permeability and low P-glycoprotein efflux in established in vitro assays, as well as quantitation of unbound drug exposure in either animal brain tissue, cerebrospinal fluid or extracellular fluid when delivered by subcutaneous or oral administration. Experiments should also demonstrate reactivation of nerve agent, or an appropriate surrogate, inhibited acetylcholinesterase either *in vitro* or *in vivo*. *In vivo* work should not only demonstrate efficacy through reactivation of brain acetylcholinesterase but the neuroprotective value should be demonstrated with pathology and behavior tests. Successful proposals will emphasize the use of *in silico*, *in vitro*, and *in vivo* methods to demonstrate efficacy of the novel compound.

Topic: NTABAA1417CBS-04

Thrust Two – Adaptive Medical Countermeasures
Enabling Science – Novel Threat Research, Systems Biology, and Applied Math Tools

Objective: The application of systems biology, computational models and predictive toxicology methodologies can be utilized to characterize chemical threat agent toxicity at the molecular, cellular and organ-system level over time. Such a comprehensive predictive toxicology tool set will significantly decrease the number of animals needed for testing and the time for assessing chemical threat agent toxicity.

The ultimate goal of this effort is to develop a tool to predict the critical pathways perturbed by each toxicant and/or class of toxicants and link these pathways to adverse health outcomes, thus allowing for evaluation of human susceptibility and enabling understanding of the effects of exposure on individuals and populations.

Computational predictive toxicology tools can characterize chemical threats if the tools are sufficiently robust and have been validated with quality *in vivo* and *in vitro* data. This topic is for proposals to develop and validate a predictive toxicology tool for multiple classes of advanced and emerging chemical threats including CWAs, NTAs, TICs, TIMs, protein and peptide toxins, etc. This tool should include methodologies for data mining, structure activity relationships (i.e., QSAR) modeling, predictive perturbations of critical cellular and tissue responses, physiologically based pharmacokinetic (PBPK) modeling and extrapolation of experimental data (*in vitro*, *in vivo*, computational or any combination thereof) to the human system.

As part of the empirical data included in validating the predictive capabilities of the model, the proposal should include *in vitro* and/or *in vivo* toxicity testing. These methods must identify and quantify key metabolic perturbations, as well as the resulting patterns and magnitudes of adverse effects that are predictive of adverse health outcomes. If the proposed effort includes *in vitro* assays, then it must be shown that the assays are already high-throughput or can be developed into high-throughput assays with meaningful output in supporting predictive toxicology tools. Tests should also address how specific biologic responses are affected by variations in the exposure scenario such as route, duration, and/or contaminants.

Proposed efforts should be designed to have a 1 year base period and up to four option years, for a maximum of up to 5 years, to fully develop and validate the predictive toxicology tool(s). Multi-disciplinary teams encompassing academia, industry and government laboratories are strongly encouraged.

Title: Predictive Toxicology Tools for Enabling Rapid Countermeasure Development

All proposals, regardless of approach (*in vitro*, *in vivo*, computational or some combination thereof) should include a section on experimental design that addresses determination of sample size and the statistical methods used to ensure power and robustness of results.

Metrics: All approaches should be aimed at the identification of primary mechanisms of action for early medical intervention to improve survival and quality of life following agent exposure. Characterization of the mechanisms of action of NTAs should identify the cellular activities and perturbations at the molecular level to support medical countermeasures development. In addition to characterizing mechanisms of action, efforts should be made to identify biomarkers of exposure that can be measured/analyzed in an operationally relevant scenario prior to onset of symptoms to support early intervention.

In vitro Toxicity Approach - Develop analytical method(s) utilizing animal and/or human cell lines to establish predictive pathway-based toxicity for assessing the biological activity of chemical threats, including NTAs, utilizing cell morphology; phenotypic and functional characterization, such as cytotoxicity vs. cell line toxicity; metabolite analysis, proteome analysis, cell line biomarkers, and/or other toxic endpoints. Proposals will only be considered responsive if they consider a suite of assays that characterize traditional CWA mechanisms of action (e.g. cholinesterase inhibition) as well as others beyond those associated with traditional agents. Such a comprehensive approach should lead to the identification of potential targets for prophylaxis or acutely administered therapeutics. Method(s) should be able to measure doses causing specific tissue perturbations (dose-response), as well as show early cellular changes leading to cell or organ injury. Methods should also determine the appropriate positive and negative controls that can be used to validate the assay results. The established methods and resulting data should be externally validated and be of sufficient quality to incorporate into the computational predictive toxicity tool. Proposals that do not address agents identified as advanced and emerging chemical threat agents by DoD will not be considered responsive to this topic.

In vivo Toxicity Approach - Develop analytical method(s) utilizing non-human vertebrates and/or invertebrates to establish pathway-based toxicity for assessing the biological activity of chemical threats, including NTAs. Proposed efforts should address 1) the specific animal model for development (species, sex and age need to be indicated and justified), as well as exposure doses, timing and routes of exposure/intoxication; 2) what biomarkers and clinical signs will be recorded (measurements may include, but not limited to, genomics, proteomics, pathophysiology, histopathology, immunology, electrophysiology, etc. at cell, tissue, organ and animal levels); and 3) the methods to determine LD_{50} (LCt_{50}) of the toxicant and ED_{50} (ECt_{50}) of the compounds and/or any possible medical countermeasures. Preference will be given to the proposals that have multi-disciplinary approaches; address pharmacokinetic-pharmacodynamic and/or toxicokinetic-toxicodynamic issues; and include analysis and archiving of multiple organs, tissues, and body fluids for future analyses by others in the Chemical and Biological Defense Program.

Predictive Toxicity Approach - The predictive toxicity tool should have a design that encompasses data mining (e.g. accessing, sorting, qualifying and prioritizing existing data, and

electronic managing) using informed searches and informed algorithms for data interpretation and integration. The chemical characterization component of the tool should include a variety of empirical and computational methods, and compounds should be organized by classes. The tool should be capable of using advances in informatics, high-throughput /high-content screening technologies and systems biology to develop robust and flexible algorithms to screen chemical threats, including NTAs, for acute toxicity. The tool should predict detailed mechanistic and dosimetry information; tissue distribution; perturbations of critical cellular responses (at molecular, cellular, and organ levels) and apply mathematical and advanced computer programs to help assess the hazard posed to individual humans, as well as populations. All predictive endpoints should be defined and tested using algorithms validated with empirical data. Third party external validation of the tools' predictive capabilities is required.

Topic: NTABAA1417CBS-05

Thrusts of Enabling Science, Threat Activity Sensing and Reporting

Objective: Develop the capability to rapidly characterize CB threat properties and to predict CB threat behavior while interacting with physical and/or biological environments. (SENSE, SHAPE, SHIELD).

Develop the capability to predict CB threat behavior while interacting with physical and/or biological environments. Accurate predictions depend on acquiring a fundamental understanding of physicochemical mechanisms (e.g., active and passive transport, reactivity) determining agent behavior.

To reach this goal, proposals are desired that result in development of ability to rapidly and quantitatively determine critical agent properties, together with enhanced understanding of fundamental physical, chemical, and biological mechanisms determining agent transport, reactivity, persistence, and availability in and on operationally relevant substrates, flora, or fauna. In addition, innovative supportive technologies that can be utilized with current or future candidates are also desired. Proposals can be structured to include up to 3 years of research tasks.

Title: Methods for Rapid Prediction of Agent-Substrate Interactions Including Correlation of Chemical or Biological Agent Physical Properties to Determine Underlying Mechanisms

This topic is to determine agent agnostic mechanisms that can be used for predicting reactivity, fate and transport of a broad range of agents under a variety of environmental conditions or dissemination modalities. Proposals aimed at identification of critical properties of chemical and biological agents that can be linked to agent behavior and fate, on and within environmental or operational substrates, will be considered. Successful Offerors will develop correlations between agent properties (e.g. hydrolysis rates and binding coefficients, vapor pressure, density, viscosity, etc.) and behavior (e.g. persistence (half-life)) or transport in the environment. The products from this effort are a critical first step in understanding and identifying the conditions and parameters that can be used for benchmarking agent fate and transport for use in predictive agent availability modeling for assessing risk. All methods and efforts should be tied to operational questions such as: (a) what is it? (b) how bad is it? (c) how is it recognized? and (d) what level of protection do current and developing countermeasures provide with respect to accomplishing military operations in a CB contaminated environment?
Successful offerings to this topic may include, but are not limited to, the following focus areas:

- Development and application of new combinatorial methods, to include physicochemical characterization, chemical synthesis, and data extraction algorithms, that permit rapid, systematic, and quantitative assessment of a broad range of variables influencing threat agent availability and hazard when present in operational environments.
- Establishment of agent baseline behavior that can serve as a standard for predicting agent behavior in other environments or environmental behavior in response to agents.

- Development and demonstration of improved modeling methods, rigorously validated by experiment, that forecast previously "unpredictable" rare events and effects due to extremes of environmental heterogeneity relevant to threat agent availability and hazard.
- Development of improved and validated correlations between (a) surface and subsurface availability of liquid and solid CB agent deposited on environmental substrates and (b) quantity and distribution of agent transferred to the skin or soldier ensemble under operational conditions.
- Novel methods for understanding CB agent interactions with indigenous cellular species of environmental flora, fauna and soil microbes, e.g. through utilization of advanced biocompatible platforms, locally controlled by an abiotic interface, that can induce and sense changes in cellular metabolism via chemical signatures.
- Modeling and testing of chemical or biological agent viability and substrate dispersion characteristics after a dissemination event (e.g. barrel bomb, IED, VED) for purposes of predictive risk modeling.
- Requirements and variables as follows:
    - Environmental variables to include, for example, substrate porosity, topology, and surface chemistry, temperature, humidity, and pH.
    - Availability parameters such as biological persistence, longevity, stability, quantitative binding constants, kinetic parameters, reaction products, permeation, surface availability, and agent interactions with various surfaces and surface characteristics/properties should be considered.
    - Predictive models will characterize mechanisms that determine agent interaction with substrates (e.g., adsorption, interstitial transport) (including interaction with additives or contaminants).
    - Data and algorithms should allow for both rapid characterization of unknown chemical or biological agents, and improvement of existing agent fate models.
    - Methods validated against lab and existing or new outdoor field studies.

Data validation should be informed by standard (e.g. ASTM) methods, and data and algorithms should be compatible with current and developing predictive models as well as applications suitable for handheld communication platforms.

Metrics:

1. Studies should characterize physiochemical properties of agent and mechanisms of agent persistence and transport under varying environmental conditions.
2. Establish predictive models/ algorithm correlations of agent behavior in the environment and in/on substrates and materials.
3. Based on agent data, establish agent agnostic predictive mechanisms.
4. Conduct independent validation studies to verify agent fate algorithm correlations by accounting for more than 90 percent of empirical agent persistence and availability
5. Validate algorithm using an unknown biological or chemical agent, - demonstrate the ability to quantify critical biological (e.g., genomics, virulence, transmissibility, longevity, stability and persistence) or physicochemical (e.g., vapor pressure, density, viscosity) properties within one month of receiving an unknown sample.